Remarks

Claims 34-42, 45 and 46 are pending. The specification has been amended to correct a typographical error in the paragraph at page 34, line 19, which discusses results with respect to viral strains P8 and D16. It is clear from reviewing Figure 6, and its depiction of graphs labeled P8 and D16, that Figure 6 is the proper figure referenced in this paragraph. Also submitted herewith is a supplemental information disclosure statement with documents referenced herein.

Claim 46 was rejected under 35 U.S.C. 112, first paragraph, as allegedly containing new matter. Applicants previously submitted declaratory evidence from Dr. Atwood showing why one of ordinary skill in the art would have understood that the application conveyed the concept of administering a pyrimidine compound without antiviral activity.

Claims 34-42 and 45 were rejected under 35 U.S.C. 103 as allegedly obvious over Weithmann (or alternatively in view of Coghlan and McChesney) in view of Hammer and Colacino. Weithmann was cited as teaching use of leflunomide to treat a disorder in which IL-1beta is involved, allegedly including HIV and hepatitis. Coghlan was cited as allegedly teaching use of leflunomide to treat hepatitis and CMV. McChesney was cited as allegedly showing that the compound A771726 is effective for preventing viral infection. Applicants disagree with the Examiner's characterization of the teaching of Weithmann, Coghlan and McChesney, for reasons of record. Applicants also note that the Examiner has not provided a reason for combining Coghlan and McChesney.

Hammer and Colacino were allegedly cited as teaching the use of pyrimidine compounds for treating viral infections. It was the Examiner's position that it would be obvious to use leflunomide for treating viral infections in combination with the compounds disclosed in Hammer or Colacino for treating viral infections.

However, Hammer's teaching addresses the use of *nucleoside analogs*. Similarly, Colacino addresses use of fialuridine (FIAU), which is a *nucleoside analog*. None of these can enhance serum levels of uridine, cytidine or thymidine, as recited in claim 34. On the contrary, the underlying concept of these *analogues* is that they interfere with the activity of naturally occurring nucleosides, either naturally occurring pyrimidines or purines. None of the references cited teach or suggest that normally occurring pyrimidines have antiviral activity, nor do they teach or suggest that administration of compounds that increase serum levels of cytidine, thymidine or uridine enhances efficacy of an antiviral.

The Examiner's position that enhancing serum levels of uridine, cytidine or thymidine is an "advantage which would flow naturally from" administration of nucleoside analogs (see paragraph 15 at page 8 of the office action) is unsupported by evidence.

The reduction in toxicity without reduction in efficacy and the ability to actually enhance efficacy by permitting higher blood concentrations of leflunomide observed upon co-administration of pyrimidine compounds that enhance serum levels of uridine, cytidine or thymidine along with the leflunomide or leflunomide analogs observed upon co-administration of leflunomide or analogs as claimed, with pyrimidine compounds that enhance serum levels of uridine, cytidine or thymidine, was unexpected. One of ordinary skill in the art would not have known which of the several effects of leflunomide would be responsible for its antiviral activity and therefore would not have known how to ameliorate toxicity without affecting antiviral efficacy.

The Examiner's offer to allow claims limited to specifically named compounds is appreciated. However, in view of the fact that other compounds useful for enhancing serum uridine levels were well known in the art before Applicants' filing date, Applicants are entitled to claims encompassing use of such compounds, including but not limited to triacetyluridine prodrugs. See, e.g., Ashour et al., *Biochemical Pharmacol.*, 51;12:1601-1611 (1996), supplied herewith. The 2', 3', 5'-tri-O-acetyluridine (TAU) prodrug referenced in Ashour et al. has been shown in human clinical trials to deliver uridine. See, e.g., Kelsen et al., *J. Clin. Oncol.*, 15:1511-1517 (1997) (Figure 1 of Hidalgo et al., *J. Clin. Oncol.* 18:167-177 (2000) shows that PN401 is 2', 3', 5'-tri-O-acetyluridine), also supplied herewith.

Also submitted herewith are excerpts from two standard chemical reference books showing the commonly accepted meaning of the terms uridine, cytidine and thymidine.

No additional fees are believed to be necessary in connection with the present submission. However, the Commissioner is hereby authorized to charge any fees due or deficiency in the fees submitted to our Deposit Account No. 13-2855, under Order No. 28385/35415.

Respectfully submitted,

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